IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of: NIKLASON et al
Serial No. 10/074,250
Filed: February 14, 2002
Title: THERAPY FOR CEREBRAL VASOSPASM

Atty Dkt. 01579-0637
C# M#
TC/A.U.: 1617
Examiner: Chong, Y.S.
Date: December 11, 2006

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

☐ **Correspondence Address Indication Form Attached.**

☐ **NOTICE OF APPEAL**
Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner twice/finally rejecting applicant's claim(s). $500.00 (1401)/$250.00 (2401) $

☒ An appeal **BRIEF** is attached in the pending appeal of the above-identified application $500.00 (1402)/$250.00 (2402) $ 250.00

☐ Credit for fees paid in prior appeal without decision on merits -$ ( )

☐ A reply brief is attached. **(no fee)**

☒ Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s)
One Month Extension $120.00 (1251)/$60.00 (2251)
Two Month Extensions $450.00 (1252)/$225.00 (2252)
Three Month Extensions $1020.00 (1253/$510.00 (2253)
Four Month Extensions $1590.00 (1254/$795.00 (2254) $ 225.00

☐ "Small entity" statement attached.

Less month extension previously paid on -$( )

TOTAL FEE (CREDIT CARD PAYMENT FORM ATTACHED) $ 475.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

901 North Glebe Road, 11th Floor
Arlington, Virginia 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100
MJW:tat

NIXON & VANDERHYE P.C.
By Atty: Mary J. Wilson, Reg. No. 32,955

Signature: Mary J. Wilson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of — Confirmation No. 5073

NIKLASON et al — Atty. Ref.: 1579-637

Serial No. 10/074,250 — TC/A.U.: 1617

Filed: February 14, 2002 — Examiner: Chong, Y.S.

For: THERAPY FOR CEREBRAL VASOSPASM

* *

12/13/2006 HMARZI1 00000008 10074250

December 11, 2006 250.00 OP

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Appellants hereby appeal the final rejection of claims 1, 10 and 11, in the Office Action dated April 10, 2006, and submit the present Appeal Brief pursuant to 37 CFR § 41.37.

Adjustment date: 12/13/2006 HMARZI1
12/12/2006 HMARZI1 00000138 10074250
01 FC:2401 -250.00 OP

Adjustment date: 12/13/2006 HMARZI1
12/12/2006 HMARZI1 00000138 10074250
01 FC:2401 -250.00 OP

12/12/2006 HMARZI1 00000138 10074250
01 FC:2401

12/12/2006 HMARZI1 00000138 10074250
225.00 OP
02 FC:2252

1148847

Table of Contents

(1) REAL PARTY IN INTEREST

The real party in interest is Duke University, Durham, North Carolina 27708-0083, by way of an Assignment from the inventors to Duke University, Durham, North Carolina 27708-0083, recorded in the U.S. Patent and Trademark Office on May 6, 2002, at Reel 012867, Frame 0391.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative, and the assignee are not aware of any related prior or pending appeals or interferences or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(3) STATUS OF THE CLAIMS

Claims 1, 10 and 11 are pending and have been finally rejected.

Claim 23 was amended in the Preliminary Amendment filed May 6, 2002. Claims 1 and 12 were amended in the Amendment filed April 15, 2004. Claims 1 and 12 were further amended in the Amendment Under Rule 116 filed May 31, 2005 and claims 24-27 were cancelled. Claims 2-9, 12-23 and 28 have been withdrawn from consideration.

Claims 1, 10 and 11 are the subject of the present appeal. A copy of claims 1, 10 and 11 is attached as a Claims Appendix, pursuant to Rule 41.37(c)(1)(viii).

(4) STATUS OF THE AMENDMENTS

The Amendment Under Rule 116 filed May 31, 2005, responsive to the final Office Action dated July 28, 2004, was entered upon the filing of a Request For Continued Examination on June 21, 2005.

An Amendment Under Rule 116 was filed July 10, 2006, in response to the final Office Action dated April 10, 2006. In the Advisory Action dated July 17, 2006, the Examiner indicated that the request for reconsideration presented in that Amendment had been considered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The present invention, as claimed in claim 1 (and claims 10 and 11 which depend therefrom), relates to a method of treating or inhibiting progression of cerebral vasospasm that follows subarochnoid hemorrhage (SAH). The method comprises administering to a patient in need of such treatment or inhibition an amount of an agent that inhibits vascular cell proliferation sufficient to effect the treatment or prevention. Support for this aspect of the invention can be found throughout the application, with particular attention being directed to page 4, lines 6-19, page 7, lines 6-12, with suitable agents being described, for example, at page 7, line 13 – page 10, line 13.

The present invention, as claimed in dependent claim 10, relates to the above-described method wherein the agent that inhibits vascular cell proliferation is a chemotherapeutic agent. Support for this aspect of the invention can be found, for example, at page 8, line 25 to page 9, line 14. The present invention, as claimed in dependent claim 11, relates to the above-described method wherein the chemotherapeutic agent is bis(chloroethyl)nitrosourea, methotrexate or 5-fluorouracil. Support for this aspect of the invention can be found, for example, at page 9, lines 2-7.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are presented for review:

Whether the invention of claim 1 lacks written description under 35 USC 112, first paragraph.

Whether claim 1 is non-enabled under 35 USC 112, first paragraph.

Whether claims 1,10 and 11 lack novelty under 35 USC 102(b) over Black (USP 5,527,778).

(7) ARGUMENT

WRITTEN DESCRIPTION (35 USC 112, FIRST PARAGRAPH)

The subject matter of claim 1 is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that, at the time the application was filed, Apellants had full possession of the claimed invention. Accordingly, reversal of the rejection is requested.

In rejecting the claims as allegedly lacking written description, the Examiner makes reference to the fact that the recited active agents are functionally defined (inhibitors of vascular cell proliferation) and further that the definitions are broad and encompass yet to be identified inhibitors. The Examiner's position appears to be that the subject disclosure would not have conveyed to the reader that Appellants had full possession of the claimed invention at the filing date.

The sufficiency of the written description provided must be viewed from the standpoint of one skilled in the art. The subject specification includes numerous examples of known agents that can be used in Appellants' novel methods. At page 7-10 of the application, a large number and wide variety of suitable agents are described. (Appellants also provide at pages 10-12 of the application methods of identifying yet further agents that would be suitable for use in the invention.) While these teachings are believed to be sufficient in and of themselves, the skilled reader would have appreciated that, as of February 2001, the art was replete with examples of agents as

defined by the instant claims. Accordingly, there is absolutely no basis for the Examiner's assertion on page 3 of the April 10, 2006 Office Action that the only suitable agents taught are those of claim 11.

The Examiner contends that the language of claim 1 is functional at the point of novelty and refers to Univ. California v Eli Lilly and Co., 43 USPQ2d 1398 (CAFC 1997). The claims of Lilly were drawn to a product (cDNA). The product was a vertebrate insulin cDNA or mammalian insulin cDNA. The court in Lilly found these recitations provided an inadequate description of the claimed genus because they did not distinguish the claimed genus from others, except by function. This is clearly a very different situation than that which exists here. Claim 1 is drawn to a method of inhibiting or treating progression of cerebral vasospasm that follows SAH. The Examiner's assertions to the contrary, the novelty of the claimed **method** does not result from the specific nature of the agent used but rather from the fact that Appellants were the first to appreciate and disclose that narrowing of cerebral arteries that is characteristic of cerebral vasospasm is in fact due to proliferation of cells in the vascular wall and/or accumulation of extracellular matrix under the influence of growth factors. Accordingly, claim 1 is in no way functional at the point of novelty.

The Examiner also relies on In re Curtis, 69 USPQ2d 1274 (CAFC 2004) and Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004) to support her assertion that the written description requirement has not been met. The portion of Curtis quoted by the

Examiner at the top of page 4 of the April 10, 2006 Office Action makes reference to the insufficiency of the disclosure of a single species to support a genus. As noted above, far more than a single species is disclosed here and thus the relevance of Curtis is not seen. In citing Noelle v. Lederman, the Examiner states at the top of page 4 of the April 10, 2006 Office Action that the court pointed out that a generic claim to anti-CD40CR Mabs lacked written description because there was no description of anti-human or other species of Mabs and no description of human CD40CR antigen. Basis for the Examiner's reliance on Noelle v. Lederman is not seen, given that the subject specification is replete with examples of known agents that could be used in the practice of the method of claim 1, and that one skilled in the art would have recognized the existence of many others (a point with which the Examiner has not disagreed).

In view of the above, reversal of the rejection are requested.

ENABLEMENT (35 USC 112, FIRST PARAGRAPH)

The subject matter of claim 1 is fully supported by an enabling disclosure. Accordingly, reversal of the rejection of claim 1 under 35 USC 112, first paragraph, as allegedly being non-enabled is requested.

In rejecting claim 1, the Examiner states, at the top of page 5 of the April 10, 2006 Office Action, that "[t]hese recitations, 'an agent that inhibits vascular proliferation' and 'a chemotherapetic agent', are seen to be merely functional

language." The Examiner contends that the instant specification fails to provide information that would allow one skilled in the art to fully practice the instant invention without undue experimentation. These comments overlook the fact that the subject disclosure includes numerous examples of agents appropriate for use in the instant invention, as well as methods of identifying yet further suitable agents.

Appellants direct attention to the court's decision in In re Angstadt and Griffin, 190 USPQ 214 (CCPA 1976) which is an enablement case that is particularly relevant to the present rejection of claim 1. In Angstadt, the court acknowledged that Appellants had not disclosed every catalyst that would work in the claimed chemical process and addressed the question of whether, in an unpredictable art, the enablement requirement of 35 USC 112, first paragraph, requires disclosure of every species encompassed by the claims. The court found that there was no such requirement, pointing out that:

> "such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed."

The court concluded that, having decided that disclosure of every species encompassed by the claims is not required, even an unpredictable art, each case must be determined on its own facts. In Angstadt, the court found that Appellants'

disclosure of a list of catalysts and details of how to make and use them to be sufficient. The court pointed out that the experimentation required to determine which species would work would not be undue and would certainly not "require ingenuity beyond that to be expected of one of ordinary skill in the art" (citing Fields v. Conover, 170 USPQ 276, 279 (CCPA 1971).

The facts in Angstadt are similar to those at hand. Here, the disclosure at pages 7-10 includes numerous types of agents suitable for use in the invention, as well as numerous examples of specific agents and still others would have been known to the skilled reader. Also included are citations for publications teaching additional specific agents (which publications are incorporated by reference at page 28). In addition, the application includes at pages 10-12 examples of methods that can be used to screen for suitable agents. Clearly, given the holding in Angstadt, nothing more should be required of Appellants.

In rejecting the claims as non-enabled, the Examiner again refers to the claims being functional at the point of novelty. If the claim were to read "A method of treating or inhibiting progression of cerebral vasospasm that follows SAH comprising administering to a patient in need of such treatment or inhibition an amount of an agent that effects said treatment or inhibition", the Examiner may have a point. Clearly such is not the case here. Appellants have come to appreciate (and disclose in the subject application) the mechanism underlying cerebral vasospasm progression

following SAH. Appellants teach in the application a large number and wide variety of agents suitable for use in treating or inhibiting such progression - claim 1 includes a generic definition of these agents.

In view of the above, reversal of the rejection is requested.

NOVELTY (35 USC 102(b)

The subject matter of claims 1, 10 and 11 is novel. Accordingly, reversal of the rejection under 35 USC 102(b) based on Black is requested.

The Examiner contends that Black discloses that well-known neuropharmaceutical agents, such as chemotherapeutic agents, are useful in treating abnormal brain tissue, including SAH. In so contending, it is clear that the Examiner has misinterpreted the reference.

Black relates to "a method for selectively opening abnormal brain tissue capillaries ... to allow selective passage of ... neuropharmaceutical agents into abnormal tissue." That is, Black describes a method to induce permeability, or "leakiness", in abnormal brain capillaries (which are roughly 10 microns in diameter). The induced "leakiness" allows the passage of therapeutic molecules into the surrounding brain tissue.

By contrast, the presently claimed method relates to the treatment or inhibition of cerebral vasospasm, which is a disease of small- to medium-sized arteries, several mm in diameter. The specific syndrome of vasospasm following SAH was poorly

understood. Appellants have realized (and disclose in the subject application) that this syndrome is caused by thickening of the wall of the artery in response to factors released during SAH. As a result of this realization, Appellants were able to teach in the instant application how to treat this syndrome, that is by blocking the growth and proliferation that occurs in the arterial wall. Thus, the claimed method, in contrast to Black, has nothing to do with capillaries, or with inducing permeability within capillaries, or with delivering drugs to injured brain tissue. Likewise, Black is unrelated to inhibiting cerebral vasospasm that results from SAH. This is underscored by the fact that figures and examples contained in Black speak to the delivery of molecules across the walls of capillary vessels.

In Black, according to the abstract and specification, "abnormal brain tissue capillaries' are "opened" in order to allow "selective passage of both low and high molecular weight neuropharmaceutical agents into the abnormal brain tissues". The clinical problem addressed by Black is the "passage of drugs into the abnormal brain tissue". Black provides a method to increase the permeability of the "abnormal brain tissue capillaries", such that drugs can pass through the wall of the capillaries and into the brain tissue. This method involves opening the abnormal brain tissue capillaries by infusing bradykinin or a bradykinin analog into the carotid artery of the mammal. The bradykinin or bradykinin analog is infused in an amount sufficient to selectively open the abnormal brain tissue capillaries to allow passage of neuropharmaceutical agents,

including high molecular weight agents, into the abnormal brain tissue without opening the normal brain capillaries to passage of the neuropharmaceutical agent. The method is indicated to be applicable to the treatment of brain tumors, abnormal tissues resulting from multiple sclerosis, ischemia and cerebral abscess. The method is also indicated to be applicable to brain tissue that is inflamed, infected or degenerated due to any number of different diseases. Examples of specific types of abnormal brain tissue are indicated to include, in addition to SAH, gliomas, metastatic brain tumors, head injury, meningitis, brain abscess and multiple sclerosis.

In the paragraph bridging columns 4 and 5 of Black, its stated:

> Any of the well known neuropharmaceutical agents may be administered in accordance with the present invention. Low molecular weight (100-20,000) as well as high molecular weight (about 20,000 to 70,000) neuropharmaceutical agents may be used. In addition to neuropharmaceutical agents, diagnostic agents may be used including imaging or contrast agents. Exemplary diagnostic agents include substances that are radioactively labelled such as 99-Tc glucoheptonate, gallium-EDTA, ferrous magnetic or iodinated contrast agents. Exemplary neuropharmaceutical agents include antibiotics, adrenergic agents, anticonvulsants, nucleotide analogs, chemotherapeutic agents, anti-trauma agents and other classes of agents used to treat or prevent neurological disorders. Specific neuropharmaceutical agents which can be administered into abnormal brain tissue in accordance with the present invention include cisplatin, carboplatin, tumor necrosis factor-α (TNF-α), methotrexate, 5-FU, amphotericin, immunotoxins, boron compounds, monoclonal antibodies and cytokines, such as interferons, interleukins, transforming growth factors, oligonucleotides.

Black in no way teaches or would have suggested that any or all of these neuropharmaceutical agents could be used to treat any or all of the abnormal brain tissues referenced above. The point of this portion of Black is that infusion of bradykinin or a bradykinin analog in accordance with the method taught by Black allows passage of whatever neuropharmaceutical agent might be necessary to treat the abnormal tissue – e.g., passage of a chemotherapeutic agent to treat a glioma or metastatic brain tumor or passage of an antibiotic to treat brain tissue that is infected.

Absolutely nothing in Black teaches administering a chemotherapeutic agent to treat SAH, as the Examiner contends. Accordingly, reversal of the rejection is requested.

In view of the foregoing, it will be clear that the claims are in condition for allowance and reversal of the final rejection is, therefore, requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: Mary J. Wilson
Mary J. Wilson
Reg. No. 32,955

MJW:tat
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

(8) CLAIMS APPENDIX

1. A method of treating or inhibiting progression of cerebral vasospasm that follows subarachnoid hemorrhage (SAH) comprising administering to a patient in need of such treatment or inhibition an amount of an agent that inhibits vascular cell proliferation sufficient to effect said treatment or inhibition.

10. The method according to claim 1 wherein said agent is a chemotherapeutic agent.

11. The method according to claim 10 wherein said chemotherapeutic agent is bis(chloroethyl)nitrosourea, methotrexate or 5-fluorouracil.

(9) EVIDENCE APPENDIX

(NONE)

(9) RELATED PROCEEDINGS APPENDIX

(NONE)